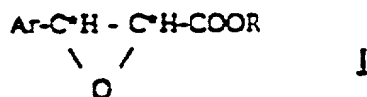


CLAIMS

1. Process for the preparation of taxane side chain precursors in which a cis- $\beta$ -arylglycidate derivative of general formula I



5 in which

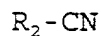
Ar represents an aryl radical and

R represents a hydrocarbon radical, preferably a linear or branched alkyl or a cycloalkyl optionally substituted by one or more alkyl

10 groups,

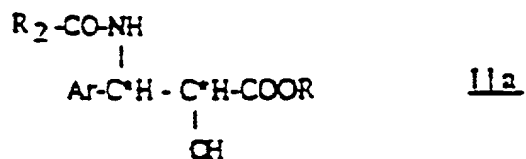
is converted, so as to regio- and stereospecifically introduce the  $\beta$ -N-alkylamide and the  $\alpha$ -hydroxyl or their cyclic precursors in a single stage by a Ritter reaction, which consists either:

15 a of the direct synthesis of a linear chain by reacting a cis- $\beta$ -arylglycidate derivative of general formula I defined above with a nitrile of formula



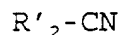
20 in which

R<sub>2</sub> represents an aryl radical, in the presence of a protonic acid and of water, in order to obtain a  $\beta$ -arylisoserine derivative of general formula IIa,



in which Ar, R and R<sub>2</sub> are defined above; or

b of the direct synthesis of a cyclic chain by reacting a cis-β-arylglycidate derivative of general formula I defined above with a nitrile of formula

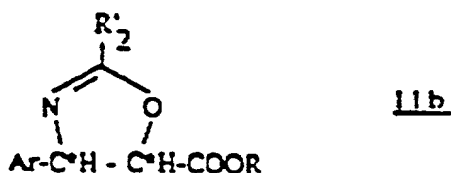


in which

R'<sub>2</sub> represents R<sub>2</sub> defined above or a lower alkyl or lower perhaloalkyl radical, such as

trichloromethyl,

in the presence of a Lewis acid or of a protonic acid, in anhydrous medium, in order to obtain the oxazoline of general formula IIb



in which Ar, R and R'<sub>2</sub> are defined above.

2. Process according to claim 1, characterized in that R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical, advantageously a cycloalkyl substituted by one or more alkyl groups, in particular a cyclohexyl.

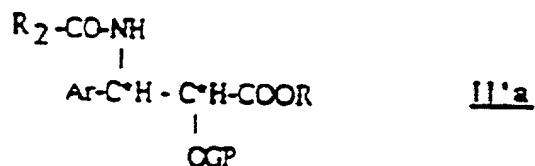
3. Process according to claim 2,  
characterized in that R is one of the enantiomers of  
the menthyl radical, in particular (+)-menthyl.

4. Process according to one of claims 1 to  
5 3, characterized in that the cis- $\beta$ -phenylglycidate  
derivative of general formula I is of (2R,3R)  
configuration and the derivatives of general formulae  
IIa and IIb obtained are of (2R,3S) configuration.

5. Process according to one of claims 1 to  
10 4, characterized in that Ar and R<sub>2</sub> represent a phenyl.

6. Process according to one of claims 1 to  
5, characterized in that the protonic acid in the stage  
a is chosen from sulphuric acid, perchloric acid or  
tetrafluoroboric acid, the Lewis acid in the stage b is  
15 chosen from the boron trifluoride acetic acid complex,  
boron trifluoride etherate, antimony pentachloride, tin  
tetrachloride or titanium tetrachloride and the  
protonic acid in the stage b is tetrafluoroboric acid.

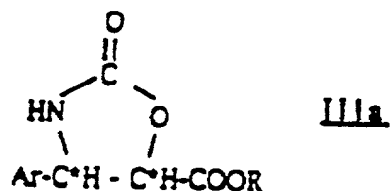
7. Process according to one of claims 1 to  
20 6, characterized in that the  $\beta$ -arylisoserine derivative  
of general formula IIa is converted by protection of  
the hydroxyl by an appropriate protective group (GP),  
in order to obtain a derivative of general formula II'a



in which

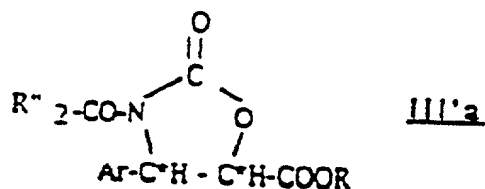
Ar, R and R<sub>2</sub> are defined above and  
GP represents a protective group for the hydroxyl  
functional group which is appropriate for the synthesis  
of taxanes, in particular chosen from alkoxy ether,  
5 aralkoxy ether, aryloxy ether or haloalkoxycarbonyl  
radicals, such as, for example, methoxymethyl,  
1-ethoxyethyl, benzyloxymethyl or (β-trimethyl-  
silylethoxy)methyl groups, tetrahydropyranyl or  
β-alkoxycarbonyl radicals, β-halogenated or alkylsilyl  
10 ethers, or alkoxyacetyl, aryloxyacetyl, haloacetyl or  
formyl radicals.

8. Process according to one of claims 1 to  
6, characterized in that the β-arylisoserine derivative  
of general formula IIa is converted into novel  
15 oxazolidinone cyclic intermediates of general formula  
IIIa



in which Ar and R are defined above  
by reacting a β-arylisoserine derivative of general  
formula IIa according to one of claims 1 to 5 with a  
20 haloalkoxycarbonyl ester, in particular 2,2,2-  
trichloroethoxycarbonyl (TrOC), and then by cyclization  
in the presence of a strong organic base, such as  
diazabicycloundecene (DBU),  
optionally converted subsequently into the

corresponding amide of general formula III'a

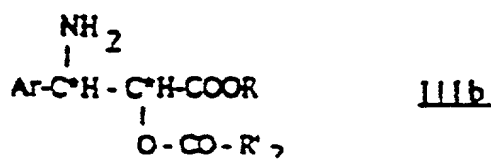


in which Ar and R are defined above and R''<sub>2</sub> represents R'<sub>2</sub> defined above, an alkoxy radical or a linear or branched alkyl radical comprising at least one

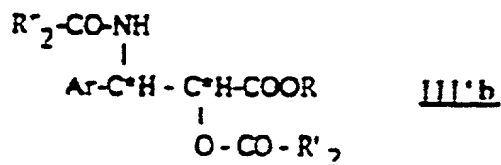
5 unsaturation.

9. Process according to one of claims 1 to 6, characterized in that the oxazoline of general formula IIb is hydrolysed in acidic medium in order to obtain the β-arylisoserine derivative of general

10 formula IIIb,



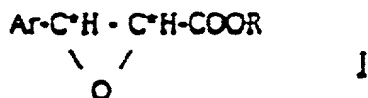
in which Ar, R and R'<sub>2</sub> are defined above, optionally converted subsequently into the corresponding amide of general formula III'b



in which Ar, R, R'<sub>2</sub> and R''<sub>2</sub> are defined above.

15 10. Process according to one of claims 1 to 9, characterized in that the cis-β-arylglycidate

derivative of general formula I



in which

Ar is defined above and

R represents an optically pure enantiomer of a  
5 highly sterically hindered chiral hydrocarbon  
radical,

is prepared by reacting the aldehyde of formula



with the haloacetate of formula

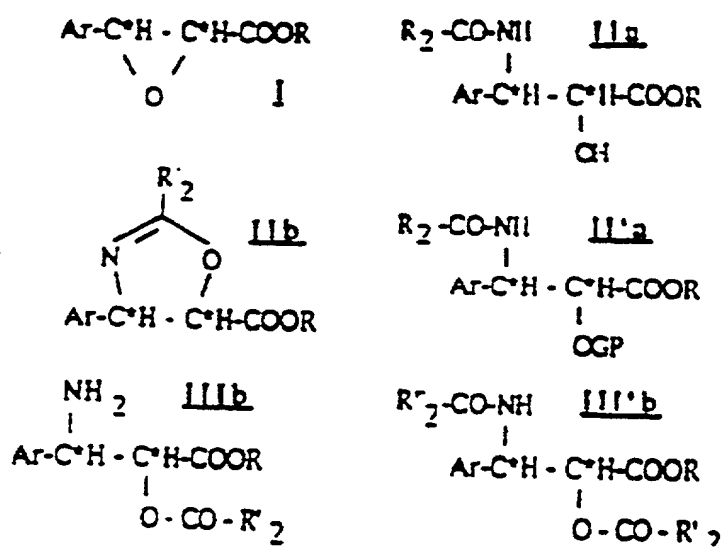


Ar and R being defined above and

X representing a halogen, in particular a chlorine  
or a bromine.

11. Process according to one of claims 1 to  
15 10, characterized in that the derivatives of formulae  
IIa, II'a, IIb, IIIa, III'a, IIIb and III'b defined  
above in which R represents a hydrogen atom are  
obtained by controlled saponification.

12. Precursor compounds of taxane side  
20 chains, characterized in that they are selected from  
the derivatives of following general formulae I, IIa,  
IIb, II'a, IIIb and III'b:



in which

Ar, R<sub>2</sub>, R'<sub>2</sub>, R''<sub>2</sub> and GP are defined in one of claims 1 to 3 and 5, and

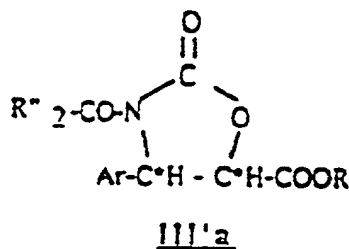
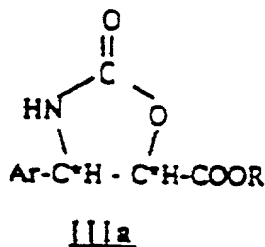
R represents an optically pure enantiomer of a highly sterically hindered chiral hydrocarbon radical.

13. Compounds according to claim 12, characterized in that R is one of the enantiomers of the menthyl radical, in particular (+)-menthyl.

14. Compounds according to either of claims 12 and 13, characterized in that the cis-β-phenylglycidate derivative of general formula I is of (2R,3R) configuration and the derivatives of general formulae IIa, IIb, IIIb and III'b are of (2R,3S) configuration.

15. Precursor compounds of taxane side chains, characterized in that they are selected from the derivatives of following general formulae IIIa and

III'a:



in which

Ar, R and R'' are defined above or R represents a hydrogen atom.

5                    16. Compounds according to claim 15,  
characterized in that they are of (2R,3S)  
configuration.

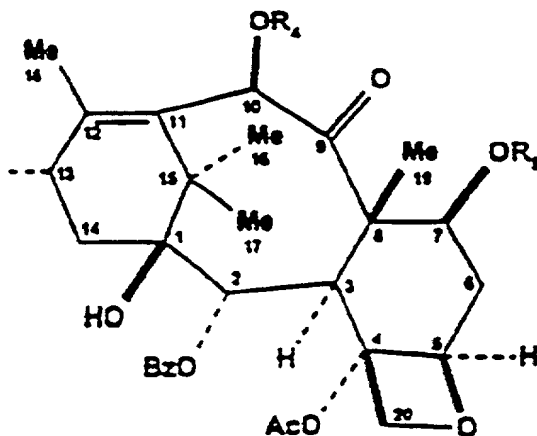
17. Process for the preparation of taxanes  
of general formula IV,

10

C-B            IV

in which

B represents a radical of general formula V



in which

Ac represents the acetyl radical,



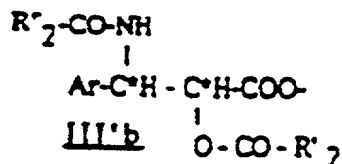
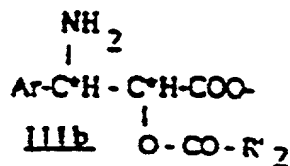
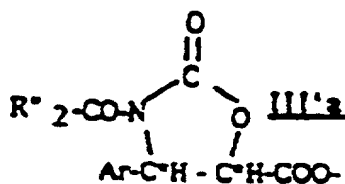
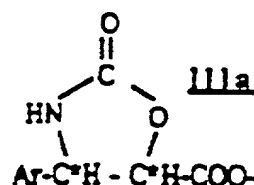
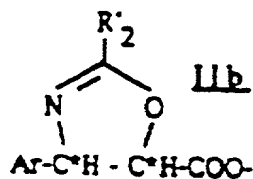
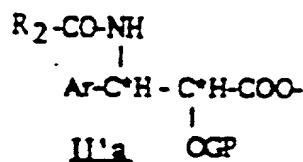
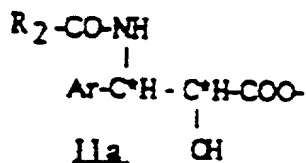
Bz represents the benzyl radical,

Me represents the methyl radical,

R<sub>4</sub> represents an acetyl radical or a protective group for the hydroxyl functional group GP1, and

5 R<sub>5</sub> represents a protective group for the hydroxyl functional group GP2, and

C represents a side chain chosen from the radicals of following formulae IIa, II'a, IIb, IIIa, III'a, IIIb and III'b:



10 in which Ar, R<sub>2</sub>, R'<sub>2</sub>, R''<sub>2</sub> and GP are defined above, by esterification of an appropriate baccatin III derivative of general formula V, carrying a C-13

hydroxyl functional group, with one of the derivatives of formulae IIa, II'a, IIb, IIIa, III'a, IIIb and III'b, for which R represents a hydrogen atom, obtained by the process according to claim 11.

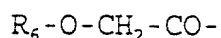
5 18. Process according to claim 17, characterized in that the GP1 and GP2 protective groups are, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as trialkylsilyls or TROC, or linear or branched bulky  
10 haloalkoxycarbonyl radicals comprising at least one halogen atom, acyl radicals in which the carbon  $\alpha$  to the carbonyl functional group carries at least one oxygen atom, or a trialkylgermanyl radical or GP1 and GP2 together form a divalent radical of formula

15 
$$-\text{SiR}_7-\text{O}-\text{SiR}_8-$$

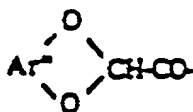
in which

R<sub>7</sub> and R<sub>8</sub>, independently of one another, represent a sterically hindered alkyl radical.

19. Process according to either of claims 17  
20 and 18, characterized in that the acyl radicals in which the carbon  $\alpha$  to the carbonyl functional group carries at least one oxygen atom are chosen from  
- alkoxy- or aryloxyacetyl radicals of formula



25 in which R<sub>6</sub> represents a sterically hindered alkyl radical, a cycloalkyl radical or an aryl radical,  
- or arylidenedioxyacetyl radicals of formula



in which Ar" represents an arylidene radical.

20. Process according to claim 19,  
characterized in that:

the sterically hindered alkyl radical is a  
5 linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl radical substituted by  
one or more bulky substituents chosen from halogens or  
linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub>  
alkoxy or C<sub>3</sub>-C<sub>6</sub> cycloalkyl or aryl radicals,

the cycloalkyl radical is a C<sub>3</sub>-C<sub>6</sub> cycloalkyl  
10 radical optionally substituted by one or more bulky  
substituents chosen from halogens or linear or branched  
C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy or aryl  
radicals, preferably a cyclohexyl radical substituted  
by one or more linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl radicals,  
15 for example menthyl, its racemate or its enantiomers  
and their mixtures in all proportions,

the aryl radical is a phenyl, naphthyl,  
anthryl or phenantryl radical optionally substituted by  
one or more bulky substituents chosen from halogens or  
20 linear or branched C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub>  
alkoxy or aryl radicals, in particular the phenyl  
radical, preferably a phenyl radical optionally  
substituted by one or two above bulky substituents  
ortho- and ortho'- to the ether bond, and

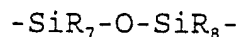
25 the arylidene radical is a phenylene,

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1 naphthylene, anthrylene or phenanthrylene radical  
optionally substituted by one or more bulky  
substituents chosen from halogens or linear or branched  
C<sub>1</sub>-C<sub>6</sub> alkyl, linear or branched C<sub>1</sub>-C<sub>6</sub> alkoxy or aryl  
5 radicals, in particular the phenyl radical.

21. Process according to either of claims 17  
and 18, characterized in that R<sub>4</sub> represents an acetyl  
radical and GP2 represents a trialkylsilyl, 2,2,2-  
trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl,  
10 2,2,2,1-tetrachloroethoxycarbonyl, 2,2,2-trichloro-t-  
butoxycarbonyl, trichloromethoxycarbonyl, phenoxyacetyl  
or trialkylgermanyl radical.

22. Process according to either of claims 17  
and 18, characterized in that R<sub>4</sub> represents a GP1 group  
15 and GP1 and GP2 represent a 2,2,2-trichloroethoxy-  
carbonyl or phenoxyacetyl radical or together form a  
divalent radical of formula



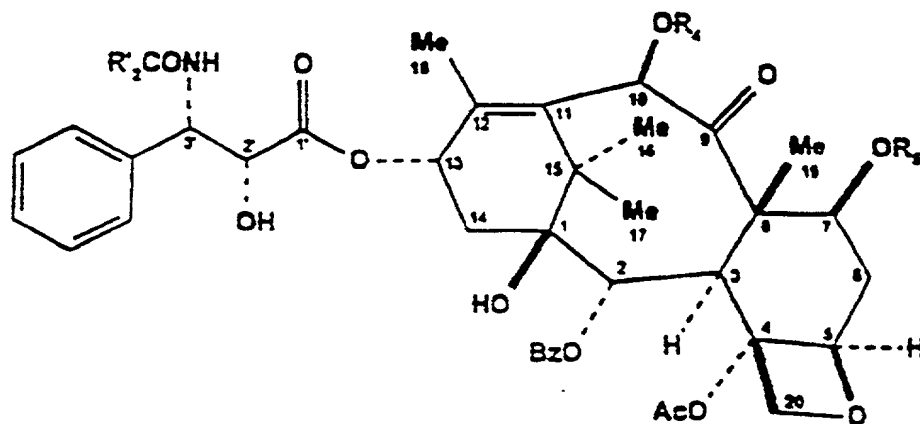
in which R<sub>7</sub> and R<sub>8</sub> each represent an isopropyl radical.

20 23. Process according to one of claims 17 to  
21, characterized in that

C represents a radical of formula IIa with Ar and  
R<sub>2</sub> representing a phenyl and  
R<sub>4</sub> represents an acetyl radical.

25 24. Process according to one of claims 17 to  
23, characterized in that, subsequently, the hydroxyls  
of the derivatives of general formula IV are

deprotected and, if appropriate, simultaneously or separately, the oxazoline ring of the radicals of formula IIb or IIIa is opened, in order to produce a taxane derivative of general formula VI



5 in which

Ac, Bz, Me and R'<sub>2</sub> are defined in one of the preceding claims,

R<sub>4</sub> represents a hydrogen atom or an acetyl radical, and

10 R<sub>5</sub> represents a hydrogen atom.

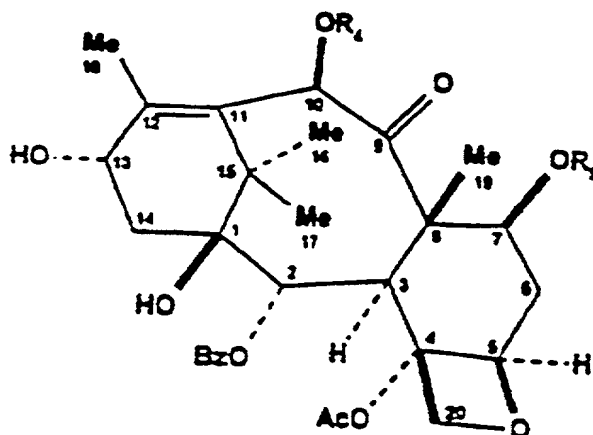
25. Taxane derivatives of general formula IV

C-B IV

in which C and B are defined in one of claims 17 to 23, with the exception of the derivatives in which C represents a radical of formula IIa, II'a, IIb, IIIb or 15 III'b, and GP1 and/or GP2 are, independently of one another, conventional groups employed in the hemisynthesis of taxanes, such as trialkylsilyls or TroC.

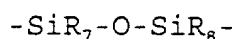
20 26. Baccatin III derivatives which are of

use in the hemisynthesis of taxanes, characterized in that they are chosen from the derivatives of general formula V



in which

- 5        Ac represents the acetyl radical,  
          Bz represents the benzyl radical,  
          Me represents the methyl radical,  
          R<sub>4</sub> represents an acetyl radical or a protective  
          group for the hydroxyl functional group GP1,  
 10       R<sub>5</sub> represents a protective group for the hydroxyl  
          functional group GP2, and  
          GP1 and GP2 are, independently of one another,  
          bulky haloalkoxycarbonyl radicals, with the  
          exception of TrOC, acyl radicals in which the  
 15       carbon  $\alpha$  to the carbonyl functional group carries  
          at least one oxygen atom, or trialkylgermanyl  
          radicals or GP1 and GP2 together form a divalent  
          radical of formula



in which

$R_7$  and  $R_8$ , independently of one another, represent a sterically hindered alkyl radical.

FOR THE "SECRET" SECTION